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(71) Applicant *(for all designated States except US)*: MASSACHUSETTS INSTITUTE OF TECHNOLOGY [US/US]; 77 Massachusetts Avenue, Cambridge, MA 02139 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: SHASTRI, Venkatram, R. [IN/US]; Apartment #16, 55 Linden Street, Allston, MA 02134 (US). HILDGEN, Patrice [CA/CA]; 779 Montee Gravel, Laval, QH7Y 2A9 (CA). SINISTERRA, Ruben, D. [CO/BR]; Apartment 301, Rua Joao Antonio Cardoso, 64, CEP-31310-390 Belo Horizonte (BR). LANGER, Robert, S. [US/US]; 77 Lombard Street, Newton, MA 02158 (US).

(74) Agents: PABST, Patrea, L. et al.; Arnall Golden & Gregory, LLP, 2800 One Atlantic Center, 1201 West Peachtree Street, Atlanta, GA 30309-3450 (US).

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(57) Abstract

Compositions which include a complex of a biologically active agent and a cyclodextrin, which is encapsulated in a polymer, and methods of preparation and use thereof are disclosed. The polymers are preferably water-insoluble, biodegradable polymers such as a polyanhydride, polyester, or polylactone. The biologically active agent includes reactive groups which would react with the polymers if it was not complexed with a cyclodextrin. In addition to minimizing or preventing interactions between the agent and the polymer, the cyclodextrin helps provide more linear release of the incorporated agent rather than burst release, acts as a surfactant to help stabilize emulsions during microparticle preparation, and allows for improved re-suspension of lyophilized microparticles relative to particles that do not include a cyclodextrin. In addition, cyclodextrin drug complexes can be loaded to contain higher concentrations of a drug than complexes without cyclodextrin. The devices and particles can be used to deliver therapeutic, prophylactic and/or diagnostic agents to a patient in need thereof.

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CYCLODEXTRIN COMPLEXES

Field of the Invention

The present application relates generally to cyclodextrin-drug complexes with enhanced controlled drug delivery.

Background of the Invention

In certain situations, the controlled delivery of a therapeutic agent is a necessity, while in other situations, controlled delivery is the only means of achieving efficacious delivery of that agent with acceptable patient compliance. Controlled delivery is of particular significance in the delivery of proteins such as insulin and growth factors, and genetic material such as recombinant DNA, where stability of the molecule and cost is an issue. Controlled delivery offers a means of not only providing a therapeutic dose of a bioactive molecule over prolonged periods, but also offers a means to minimize the dose and potential harmful side effects and localize the therapy.

A number of drug delivery systems have been investigated, including polymer microcapsules, microparticles, liposomes and emulsions. Many of these are prepared from synthetic biodegradable polymers such as polyanhydrides and poly(hydroxy acids). However, these materials may react with the drugs to be delivered. For example, proteins contain amine groups which may interact with anhydride groups present on polyanhydrides and ester groups on polyesters such as those formed from hydroxy acids. Further, it is often difficult to obtain linear release kinetics, without having burst release of an agent incorporated into a drug delivery device.

The efficiency of a polymer based drug delivery system is dependent on various factors such as the stability of the bioactive molecule in the polymer matrix as well as interactions with the matrix. The interaction of the bioactive molecule with the polymer in some cases is *via* a chemical reaction resulting in the covalent binding of the molecule to the polymer backbone with subsequent loss in the molecular weight of the polymer. This can significantly alter release kinetics of the molecule. In the case of proteins,

alteration of the chemical nature of the side chain of amino acid residues such as a lysine, cysteine, etc., via a chemical reaction with the polymer could result in irreversible changes in the tertiary structure of the protein resulting in the denaturation of the protein. Furthermore, interaction of hydrophobic residues, such as tryptophan, in the protein backbone with hydrophobic regions in the polymer could also result in conformational changes. Conformational changes in proteins in most cases is accompanied by a loss or diminution of activity. Therefore, these problems have to be addressed in order to develop efficient delivery vehicles .

The reactivity of therapeutic agent with the polymer is of even greater concern when the polymer backbone is highly reactive as in the case of the polyanhydrides. Polyanhydrides, which belong to the class of biocompatible and biodegradable polymers, have been extensively investigated as vehicles for controlled delivery of therapeutic agents due their ability to undergo surface degradation. Tamada and Langer, *J. Biomater. Sci. Polym. Edn*, 3(4):315-353. The surface erosion of the polymer results in a zero-order release of the therapeutic agent from the polymer which is highly desirable in treatment of chronic ailments. However, the desired release kinetics can be significantly altered if the therapeutic agent of interest reacts with the polymer. Amine containing drugs and peptide hormones, such as insulin, chemically interact and react with polyanhydrides. Leong et al., *Biomed. Mat. Res*, 20: 51-64. Ron, *Proc. Natl. Acad. Sci USA*, 90: 4176-4180. In the case of insulin, denaturation of the protein during release from polyanhydride (poly(p-carboxyphenoxy hexane (CPH)) matrices was observed as indicated by the formation of aggregates. Li et al. have shown that the incorporation of caffeine base in poly(D,L-lactic acid) enhances the degradation rate of the polymer. Li et al., *J. Controlled. Rel.*, 40:41-53. Hence, there exists a need to prevent undesirable interactions between the therapeutic agent and the polymer matrix.

Numerous references disclose particles which include cyclodextrins for drug delivery. U.S. Patent No. 4,925,678 to Ranney discloses coatings and matrix materials which include drugs or diagnostic agents, such as cyclodextrin. U.S. Patent No. 5,506,203 to Backstrom et al. discloses

methods of treating patients in need of insulin treatment by administering a dry powder via inhalation along with an enhancer compound, such as a cyclodextrin. U.S. Patent No. 5,534,496 to Lee et al. discloses tablets formed with a drug trapped inside a uniform coating of peptides in a cyclodextrin matrix. U.S. Patent No. 5,582,836 to Carli et al. discloses transdermal therapeutic compositions including drugs which are incorporated into microparticles prepared from polymeric cyclodextrins. U.S. Patent No. 5,595,762 to Derrieu discloses compositions including active agents which are stabilized by coating them in film-forming agents such as polyvinyl pyrrolidones, polyvinyl alcohols, and other water-soluble polymers. The agents can then be sequestered in cyclodextrins. PCT WO 96/28143 by Boeringer Mannheim discloses polypeptide-containing microparticles which can include additives such as cyclodextrins. PCT WO 97/04747 by Dunn discloses particles for the delivery of large macromolecules, which are entrapped in biodegradable hydrogel polymers. The macromolecules can be complexed with cyclodextrins, which are then encapsulated into nanoparticles with biodegradable water-soluble hydrogel polymers.

It would be advantageous to provide drug delivery formulations wherein interactions between the drug and the polymeric material are minimized or eliminated. It would also be advantageous to provide formulations which minimize burst release of encapsulated agents.

It is therefore an object of the present invention to provide means for minimizing or reducing drug-polymer interactions in polymeric drug delivery formulations. It is a further object of the present invention to provide polymeric compositions which minimize the burst effect typically observed with many drug delivery devices.

Summary of the Invention

Compositions which include a complex of a biologically active agent and a cyclodextrin, which can be encapsulated in a polymeric microparticle or other polymeric device, and methods of preparation and use thereof are disclosed. The compositions are prepared from a water-insoluble, biodegradable polymer such as a polyanhydride, polyester, or polylactone.

The biologically active agent is an agent which includes reactive groups which could react with the polymers if they were not complexed with a cyclodextrin. In addition to minimizing or preventing interactions between the agent and the polymer, the cyclodextrin helps provide linear release of the incorporated agent rather than a burst release, acts as a surfactant to help stabilize emulsions during microparticle preparation, and allows for improved re-suspension of lyophilized microparticles relative to particles that do not include a cyclodextrin. In addition, in some cases, cyclodextrin drug complexes can be loaded to contain higher concentrations of a drug than complexes without cyclodextrin.

The devices and microparticles can be prepared using known methodology, taking care not to denature the incorporated agent. Preferred methods of preparing the microparticles are by spray drying or emulsion techniques. The devices and particles are used to deliver therapeutic, prophylactic and/or diagnostic agents to a patient in need thereof. Examples of useful drugs that can be delivered in an enhanced manner include antibiotics such as chlorhexidine and anticancer compounds such as the rhodium (II) carboxylates and their derivatives.

Brief Description of the Drawings

Figure 1 is a graph comparing release of uncomplexed chlorhexidine (white triangles), chlorhexidine complexed with beta cyclodextrin (BCD) (black diamonds), and chlorhexidine complexed with hydroxypropyl beta cyclodextrin (HPBCD) (black squares) from poly(D,L-lactic-co-glycolic acid) ("PLGA") microspheres.

Detailed Description of the Invention

Formulations have been developed based on cyclodextrin complexes which are then encapsulated in polymer. These complexes prevent reactions between the polymer and the encapsulated agent.

I. Cyclodextrin Complexes

A. Agents

Any of a variety of therapeutic, prophylactic or diagnostic agents can be complexed with a cyclodextrin for local or systematic delivery. Active agents which have a group which is potentially reactive with a polymer, for example, drugs which have amino, carboxyl, sulfhydryl, or sulfonyl groups, are particularly useful to form cyclodextrin complexes. Examples of agents include synthetic inorganic and organic compounds, proteins and peptides, polysaccharides and other sugars, lipids, and nucleic acid sequences having therapeutic, prophylactic or diagnostic activities. Nucleic acid sequences include genes, antisense molecules which bind to complementary DNA to inhibit transcription, and ribozymes. Proteins are defined as consisting of 100 amino acid residues or more; peptides are less than 100 amino acid residues. Unless otherwise stated, the term protein refers to both proteins and peptides. Examples include insulin and other hormones. The agents to be incorporated can have any of a variety of biological activities, such as vasoactive agents, neuroactive agents, hormones, anticoagulants, immunomodulating agents, cytotoxic agents, prophylactic agents, antibiotics, antivirals, antisense, antigens, and antibodies. Compounds can be of a wide range of molecular weights, for example, between 100 and 500,000 grams per mole.

The examples demonstrate complexation of an antibiotic, chlorhexidine, in a formulation which is particularly useful in treatment of periodontal disease. Rhodium(II) citrate, a transition metal anticancer compound which chelates DNA, has been complexed with a cyclodextrin, hydroxypropyl-beta-cyclodextrin as a means to improve encapsulation and release kinetics from poly(dl-lactic-co-glycolic) acid ("PLGA") and poly(anhydride) microspheres. The complexation of rhodium(II) citrate with hydroxypropyl-beta-cyclodextrin significantly increased both the encapsulation efficiency and duration of release in both polymer systems.

B. Cyclodextrins

Cyclodextrins are a family of crystalline molecules that include a chain of six, seven or eight glucopyranose units that are joined to one another

at their terminal ends. Due to steric interactions, cyclodextrins form a cyclic structure of torus-shaped macro-rings which have an internal axial cavity. The outer surface of these molecules is hydrophilic, and the internal cavity is apolar.

Cyclodextrins form complexes with various drug molecules. The complex is useful in preventing or minimizing interactions between the biologically active agent and a polymer. These interactions are particularly deleterious when the biologically active material includes reactive groups such as, for example, amine groups of a protein or peptide, and the polymer is a biodegradable polymer such as a polyanhydride, polyester, polycarbonate, or other polymer which contains functional groups which react with amine groups.

Other advantages of including a cyclodextrin in the formulation are that the cyclodextrin can act as a surfactant for the microparticles, as an emulsion stabilizer during particle preparation, and also can allow for improved re-suspension of lyophilized microparticles prior to injection. Still another advantage is that cyclodextrins can increase encapsulation efficiency (loading) of water soluble drugs in hydrophobic polymers when using double emulsion systems.

Any cyclodextrin can be used which reacts with one or more groups on the agent to be incorporated to form a complex, which acts as a suitable surfactant during the preparation of the particles, or which allows lyophilized particles to re-suspend without significant agglomeration or aggregation. The cyclodextrins are preferably pyrogen free. Suitable cyclodextrins are disclosed, for example, in PCT WO 96/20222 by Solvay, the contents of which are hereby incorporated by reference. Examples of pyrogen free cyclodextrins include alpha cyclodextrin, gamma cyclodextrin, hydroxypropyl alpha cyclodextrin, hydroxypropyl beta cyclodextrin, and hydroxypropyl gamma cyclodextrin.

The cyclodextrins can be water-soluble. Examples of water-soluble cyclodextrins include hydroxyethyl alpha cyclodextrin, hydroxyethyl beta cyclodextrin, hydroxyethyl gamma cyclodextrin, hydroxypropyl alpha cyclodextrin, hydroxypropyl beta cyclodextrin, hydroxypropyl gamma

cyclodextrin, methylated beta cyclodextrin, trimethyl beta cyclodextrin, tertiary amine beta cyclodextrin, sulfated alpha cyclodextrin, sulfated beta cyclodextrin, sulfated gamma cyclodextrin, and sulfated delta cyclodextrin.

The cyclodextrins can be water-insoluble. Examples of water-insoluble cyclodextrins include acetylated alpha cyclodextrin, acetylated beta cyclodextrin, acetylated gamma cyclodextrin, hexylated beta cyclodextrin, 2-ethylhexylglycidyl ether beta cyclodextrin, C-6 monohexyl sulfide beta cyclodextrin, C-6 mono-para-toluene sulfonate beta cyclodextrin.

The cyclodextrins can be anionic. Examples of anionic cyclodextrins include sulfated beta cyclodextrin, sulfated alpha cyclodextrin, sulfated gamma cyclodextrin, octenylsuccinylated beta cyclodextrin, carboxymethyl alpha cyclodextrin, carboxymethyl beta cyclodextrin, succinylated beta cyclodextrin.

The cyclodextrins can be cationic. Examples of cationic cyclodextrins include quaternary ammonium alpha cyclodextrin, quaternary ammonium beta cyclodextrin, and quaternary ammonium gammacyclodextrin.

The cyclodextrins can also be amphoteric. Examples of amphoteric cyclodextrins include quaternary ammonium carboxymethyl beta cyclodextrin and tertiary amine carboxymethyl beta cyclodextrin.

Preferred cyclodextrins are methylated cyclodextrins, hydroxypropyl cyclodextrins, hydroxyethyl cyclodextrins, quaternary ammonium cyclodextrins, and sulfated cyclodextrins. Most preferred are hydroxypropyl cyclodextrin and quaternary ammonium cyclodextrins.

C. Polymeric Composition

Polymeric compositions may be formed from any biocompatible, and preferably biodegradable, polymer, copolymer, or polymer blend. Preferred polymers are those which are capable of degrading *in vivo* over a course of hours to months, depending on the desired rate of drug delivery. The polymers may be tailored to optimize different characteristics of the particle including: i) interactions between the agent to be delivered and the polymer to provide stabilization of the agent and retention of activity upon delivery; ii) rate of polymer degradation and, thereby, rate of drug release profiles; iii)

surface characteristics and targeting capabilities via chemical modification; and iv) device porosity.

Surface eroding polymers such as polyanhydrides may be used to form the particles. For example, polyanhydrides such as poly[(*p*-carboxyphenoxy)-hexane anhydride] (PCPH) may be used. Biodegradable polyanhydrides are described in U.S. Patent No. 4,857,311, to Domb et al., the contents of which are incorporated herein by reference.

In another embodiment, bulk eroding polymers such as those based on polyesters, including poly(hydroxy acids) can be used. For example, polyglycolic acid (PGA), polylactic acid (PLA), or copolymers thereof may be used to form the particles. The polyester may also have a charged or functionalizable group, such as an amino acid. In a preferred embodiment, particles with controlled release properties can be formed of poly(D,L-lactic acid) and/or poly(D,L-lactic-co-glycolic acid) ("PLGA") which incorporate a surfactant such as dipalmitoyl phosphatidylcholine ("DPPC").

Other useful polymers include polyamides, polycarbonates, polyalkylenes such as polyethylene, polypropylene, poly(ethylene glycol), poly(ethylene oxide), poly(ethylene terephthalate), poly vinyl compounds such as polyvinyl alcohols, polyvinyl ethers, and polyvinyl esters, polymers of acrylic and methacrylic acids, polyphosphates, polyphosphonates, polyorthoesters, polyphosphazenes, celluloses and other polysaccharides, and peptides or proteins, or copolymers or blends thereof. Polymers may be selected with, or modified to have, the appropriate stability and degradation rates *in vivo* for different controlled drug delivery applications. Materials other than biodegradable polymers may be used to form the particles. Suitable materials include various non-biodegradable polymers and various excipients.

D. Other Components

Excipients

In addition to the encapsulated complex, the device can include one or more excipients such as a sugar, such as lactose, a protein, such as gelatin or albumin, and/or a surfactant.

Surfactants

As used herein, the term "surfactant" refers to any agent which preferentially absorbs to an interface between two immiscible phases, such as the interface between water and an organic polymer solution, a water/air interface or organic solvent/air interface. Surfactants generally possess a hydrophilic moiety and a lipophilic moiety, such that, upon absorbing to microparticles, they tend to present moieties to the external environment that do not attract similarly-coated particles, thus reducing particle agglomeration. Surfactants may also promote absorption of the encapsulated agent and increase bioavailability of the agent.

As used herein, a particle "incorporating a surfactant" refers to a particle with a surfactant on at least the surface of the particle. The surfactant may be incorporated throughout the particle and on the surface during particle formation, or may be coated on the particle after particle formation. The surfactant can be coated on the particle surface by adsorption, ionic or covalent attachment, or physically "entrapped" by the surrounding matrix. The surfactant can be, for example, incorporated into controlled release particles, such as polymeric microspheres.

Providing a surfactant on the surfaces of the particles can reduce the tendency of the particles to agglomerate due to interactions such as electrostatic interactions, Van der Waals forces, and capillary action. The presence of the surfactant on the particle surface can provide increased surface rugosity (roughness), thereby reducing the surface area available for intimate particle-particle interaction.

Surfactants known in the art can be used including any naturally occurring surfactant. Other exemplary surfactants include phosphogycerides; hexadecanol; fatty alcohols such as polyethylene glycol (PEG); polyoxyethylene-9-lauryl ether; a surface active fatty acid, such as palmitic acid or oleic acid; sorbitan trioleate (Span 85); glycocholate; surfactin; a poloxomer; a sorbitan fatty acid ester such as sorbitan trioleate; tyloxapol and phospholipids.

II. Formation of Polymeric Devices

Polymeric devices may be prepared using standard techniques. In the preferred embodiment, the devices are particles, between 25 and 1000 μm in diameter. These particles can be formed by single and double emulsion solvent evaporation, spray drying, solvent extraction, solvent evaporation, phase separation, simple or complex coacervation, interfacial polymerization, or other methods well known to those of ordinary skill in the art. Preferred methods for preparing the particles are spray drying and double emulsion techniques.

Methods developed for making microspheres for delivery of encapsulated agents are described in the literature, for example, as described in Doubrow, M., Ed., "Microcapsules and Nanoparticles in Medicine and Pharmacy," CRC Press, Boca Raton, 1992. Methods also are described in Mathiowitz and Langer, *J. Controlled Release*, 5:13-22 (1987); Mathiowitz *et al.*, *Reactive Polymers*, 6:275-283 (1987); and Mathiowitz *et al.*, *J. Appl. Polymer Sci.*, 35:755-774 (1988). The selection of the method depends on the polymer selection, the size, external morphology, and crystallinity that is desired, as described, for example, by Mathiowitz *et al.*, *Scanning Microscopy*, 4: 329-340 (1990); Mathiowitz *et al.*, *J. Appl. Polymer Sci.*, 45:125-134 (1992); and Benita *et al.*, *J. Pharm. Sci.* 73:1721-1724 (1984).

Solvent evaporation is described, for example, in Mathiowitz *et al.*, (1990), Benita; and U.S. Patent No. 4,272,398 to Jaffe. With some polymeric systems, polymeric particles prepared using a single or double emulsion technique vary in size depending on the size of the droplets. If droplets in water-in-oil emulsions are not of a suitably small size to form particles with the desired size range, smaller droplets can be prepared, for example, by sonication or homogenization of the emulsion, or by the addition of surfactants. Methods of spray drying are disclosed in PCT WO 96/09814 by Sutton and Johnson.

If the particles prepared by any of the above methods have a size range outside of the desired range, particles can be sized, for example, using a sieve, and further separated according to density using techniques known to those of skill in the art.

III. Drug Administration

The polymeric composition may be administered alone or in any appropriate pharmaceutically acceptable carrier, such as a liquid, for example saline, or as a powder. Devices can be implanted or injected. Particles can be administered via injection, for example, subcutaneous, intravenous, intraperitoneal, or intramuscular injection, orally, via inhalation, transmucosally, or other means known to those of skill in the art. Appropriate dosage, formulations and delivery systems may be selected for a particular application, taking into consideration the dosage regimens and other pertinent information.

In one preferred embodiment, the agent that is complexed with the cyclodextrin and formed into the microparticle is one that is useful for the treatment or prophylaxis of periodontic disease. An example of such an agent is an antibiotic, chlorhexidine, although other useful agents are well known to those of skill in the art. The microspheres are administered to the mucosal tissue surrounding the teeth.

The present invention will be further understood by reference to the following non-limiting examples.

Example 1: Chlorhexidine Release from PLGA Microspheres

Inclusion complexes of chlorhexidine and beta cyclodextrin (BCD) and hydroxypropyl beta cyclodextrin (HPBCD) were prepared by freeze drying a 1:1 molar ratio of digluconate of chlorhexidine and the cyclodextrin. PLGA microspheres including chlorhexidine alone and which include the two complexes were prepared by double emulsion (w/o/w)/solvent evaporation technique. O'Donnell and McGinity, *Advance Drug Delivery Reviews*, 25-42 (1997). The microspheres were characterized for size and morphology using a Coulter Counter particle sizer and by Scanning Electron Microscopy. The average particle size of the microspheres was 30 μm for chlorhexidine alone, 15 μm for the BCD complex, and 10 μm for the HPBCD complex.

The release of chlorhexidine from the microspheres was evaluated, and the results are shown in Figure 1. Microspheres including uncomplexed

chlorhexidine (white triangles) showed a large burst effect (43% of loading), whereas the microspheres including complexed chlorhexidine (black diamonds and black squares) showed a negligible burst effect.

Chlorhexidine complexed with BCD (black diamonds) demonstrated release over a longer period of time than chlorhexidine complexed with HPBCD (black squares). This data demonstrates that inclusion complexes of drugs and cyclodextrins can be used to deliver the complexed drugs in a controlled manner without a burst effect.

We claim:

1. A polymeric composition comprising an agent complexed with a cyclodextrin which is dispersed within a polymer wherein the agent comprises groups reacting with groups on the polymer and these groups on the agent are complexed with cyclodextrin.

2. The composition of claim 1 wherein the polymer is selected from the group consisting of polyhydroxy acids, polyanhydrides, polyorthoesters, polyesters, polyphosphazenes, and copolymers and blends of these polymers.

3. The composition of claim 1 wherein the polymer is non-biodegradable.

4. The composition of claim 1 in the form of microparticles.

5. The composition of claim 1 wherein the agent contains groups reactive with the polymer selected from the group consisting of amino, carboxyl, sulfhydryl, and sulfonyl groups.

6. The composition of claim 1 wherein the cyclodextrin is selected from a group consisting of pyrogen free, water-soluble, water-insoluble, anionic, cationic, and amphoteric cyclodextrins.

7. The composition of claim 1 further comprising an excipient or a surfactant.

8. The composition of claim 1 wherein the release of the incorporated agent approximates zero order or first order release.

9. The composition of claim 1 wherein the agent is a drug.

10. A method for delivering an agent to a patient in need thereof wherein the agent is complexed with a cyclodextrin which is dispersed within a polymer wherein the agent comprises groups reacting with groups on the polymer and these groups on the agent are complexed with cyclodextrin.

11. The method of claim 10 wherein the polymer is in the form of a microparticle.

12. The method of claim 11 wherein the microparticles are administered by injection.

13. The method of claim 11 wherein the microparticles are administered orally.

14. The method of claim 11 wherein the microparticles are administered topically.

15. The method of claim 11 wherein the polymer is selected from the group consisting of polyhydroxy acids, polyanhydrides, polyorthoesters, polyesters, polyphosphazenes, and copolymers and blends of these polymers.

16. The method of claim 11 wherein the agent contains groups reactive with the polymer selected from the group consisting of amino, carboxyl, sulfhydryl, and sulfonyl groups.

17. The method of claim 11 wherein the cyclodextrin is selected from a group consisting of pyrogen free, water-soluble, water-insoluble, anionic, cationic, and amphoteric cyclodextrins.

18. The method of claim 11 wherein the agent is selected from a group consisting of synthetic inorganic and organic compounds, proteins and peptides, polysaccharides and other sugars, lipids, and nucleic acid sequences.

19. The method of claim 11 wherein the agent is delivered for the treatment of periodontal disease.

20. The method of claim 18 wherein the agent is a anti-cancer therapeutic.

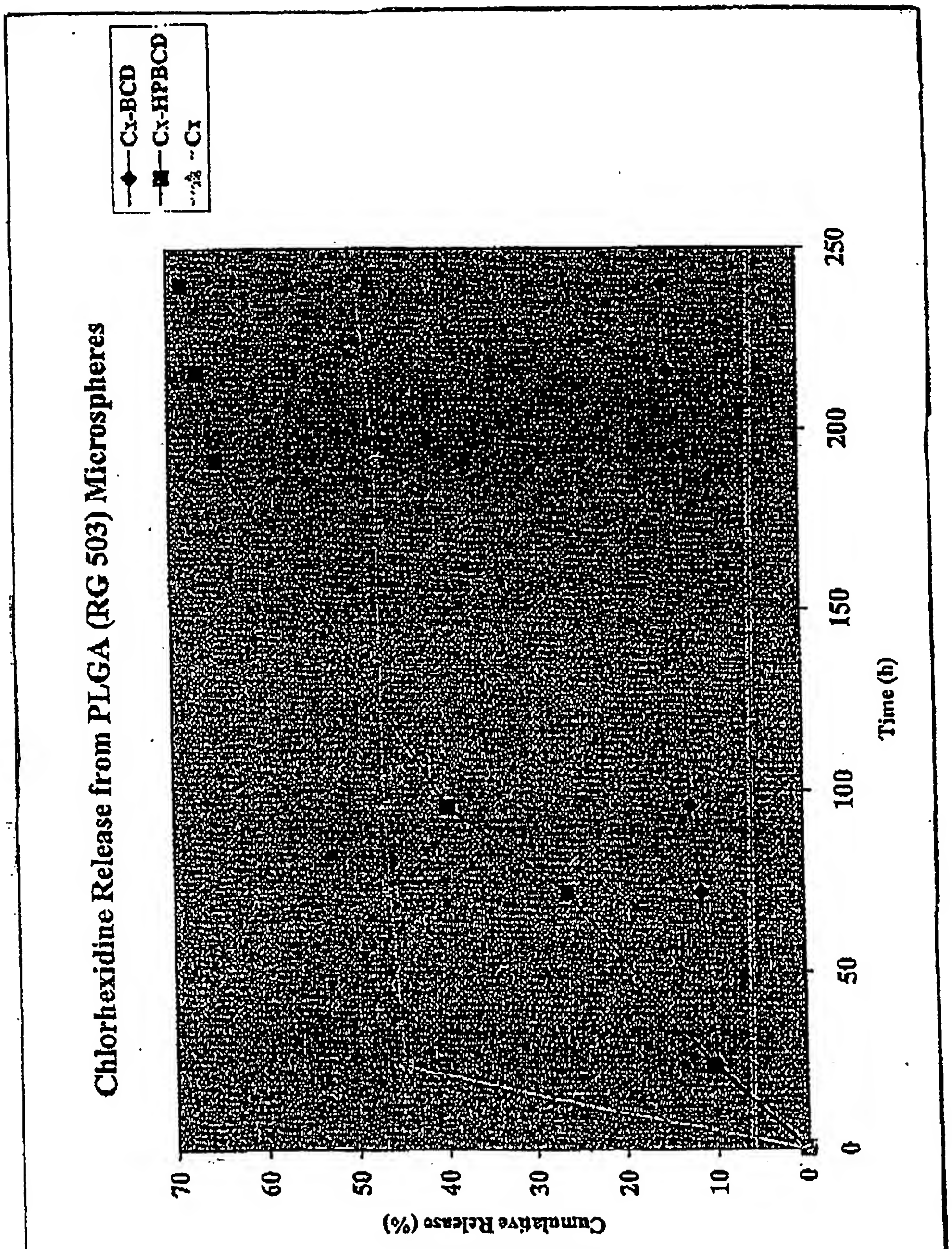
Chlorhexidine Release from PLGA (RG 503) Microspheres
Cx-BCD
Cx-HPBCD
Cx
Cumulative Release (%)
70
60
50
40
30
20
10
0
Time (h)
0
50
100
150
200
250

FIGURE 1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/11981

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	SINISTERRA, RUBEN DARIO ET AL: "Encapsulation and Release of Rhodium(II) Citrate and Its Association Complex with Hydroxypropyl-.beta.- cyclodextrin from Biodegradable Polymer Microspheres" J. PHARM. SCI. (1999), 88(5), 574-576, XP000823551 see the whole document ---	1-20
Y	WO 95 11665 A (VIRBAC LAB ;DERRIEU GUY (FR); AUBERT ANDRE (FR); RAYNIER BERNARD () 4 May 1995 see the whole document; claims; example 1 ---	1-20
X,Y	EP 0 745 381 A (TECNIMEDE SOCIEDADE TECNICO ME) 4 December 1996 see the whole document; claims; example 1 --- -/--	1-20

[X] Further documents are listed in the continuation of box C.

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13 September 1999	23 September 1999 (23.09.99)

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European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	BERTE, M

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 241 806 A (FUJISAWA PHARMACEUTICAL CO) 21 October 1987 see the whole document; claims; example 1 ---	1-20
X	EP 0 193 164 A (FUJISAWA PHARMACEUTICAL CO) 3 September 1986 see the whole document; claims; example 1 -----	1

1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/11981

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 241 806 A (FUJISAWA PHARMACEUTICAL CO) 21 October 1987 see the whole document; claims; example 1 ---	1-20
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INTERNATIONAL SEARCH REPORT

I ational application No.
PCT/US 99/11981

Box I Observations where certain claims were found unsearchable (C ntinuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 10-20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

.ormation on patent family members

Interr ·'onal Application No
PCT/US 99/11981

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 9511665	A	04-05-1995	FR	2711525	A	05-05-1995
			AT	181500	T	15-07-1999
			AU	688408	B	12-03-1998
			AU	8109294	A	22-05-1995
			CA	2175077	A	04-05-1995
			DE	69419260	D	29-07-1999
			DE	725627	T	30-04-1997
			EP	0725627	A	14-08-1996
			ES	2095819	T	01-03-1997
			JP	9505564	T	03-06-1997
			NZ	275837	A	24-11-1997
			US	5683722	A	04-11-1997
EP 0745381	A	04-12-1996	NONE			
EP 0241806	A	21-10-1987	JP	63045219	A	26-02-1988
			US	4749574	A	07-06-1988
EP 0193164	A	03-09-1986	JP	62000015	A	06-01-1987

CORRECTED VERSION*

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(71) Applicant (*for all designated States except US*): MASSACHUSETTS INSTITUTE OF TECHNOLOGY [US/US]; 77 Massachusetts Avenue, Cambridge, MA 02139 (US).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): SHASTRI, Venkatram, R. [IN/US]; Apartment #16, 55 Linden Street, Allston, MA 02134 (US). HILDGEN, Patrice [CA/CA]; 779 Montee Gravel, Laval, QH7Y 2A9 (CA). SINISTERRA, Ruben, D. [CO/BR]; Apartment 301, Rua Joao Antonio Cardoso, 64, CEP-31310-390 Belo Horizonte (BR). LANGER, Robert, S. [US/US]; 77 Lombard Street, Newton, MA 02158 (US).

(74) Agents: PABST, Patrea, L. et al.; Arnall Golden & Gregory, LLP, 2800 One Atlantic Center, 1201 West Peachtree Street, Atlanta, GA 30309-3450 (US).

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(54) Title: CYCLODEXTRIN COMPLEXES

(57) Abstract

Compositions which include a complex of a biologically active agent and a cyclodextrin, which is encapsulated in a polymer, and methods of preparation and use thereof are disclosed. The polymers are preferably water-insoluble, biodegradable polymers such as a polyanhydride, polyester, or polylactone. The biologically active agent includes reactive groups which would react with the polymers if it was not complexed with a cyclodextrin. In addition to minimizing or preventing interactions between the agent and the polymer, the cyclodextrin helps provide more linear release of the incorporated agent rather than burst release, acts as a surfactant to help stabilize emulsions during microparticle preparation, and allows for improved re-suspension of lyophilized microparticles relative to particles that do not include a cyclodextrin. In addition, cyclodextrin drug complexes can be loaded to contain higher concentrations of a drug than complexes without cyclodextrin. The devices and particles can be used to deliver therapeutic, prophylactic and/or diagnostic agents to a patient in need thereof.

*(Referred to in PCT Gazette No. 23/2000, Section II)

CYCLODEXTRIN COMPLEXES

Field of the Invention

The present application relates generally to cyclodextrin-drug complexes with enhanced controlled drug delivery.

Background of the Invention

In certain situations, the controlled delivery of a therapeutic agent is a necessity, while in other situations, controlled delivery is the only means of achieving efficacious delivery of that agent with acceptable patient compliance. Controlled delivery is of particular significance in the delivery of proteins such as insulin and growth factors, and genetic material such as recombinant DNA, where stability of the molecule and cost is an issue. Controlled delivery offers a means of not only providing a therapeutic dose of a bioactive molecule over prolonged periods, but also offers a means to minimize the dose and potential harmful side effects and localize the therapy.

A number of drug delivery systems have been investigated, including polymer microcapsules, microparticles, liposomes and emulsions. Many of these are prepared from synthetic biodegradable polymers such as polyanhydrides and poly(hydroxy acids). However, these materials may react with the drugs to be delivered. For example, proteins contain amine groups which may interact with anhydride groups present on polyanhydrides and ester groups on polyesters such as those formed from hydroxy acids. Further, it is often difficult to obtain linear release kinetics, without having burst release of an agent incorporated into a drug delivery device.

The efficiency of a polymer based drug delivery system is dependent on various factors such as the stability of the bioactive molecule in the polymer matrix as well as interactions with the matrix. The interaction of the bioactive molecule with the polymer in some cases is *via* a chemical reaction resulting in the covalent binding of the molecule to the polymer backbone with subsequent loss in the molecular weight of the polymer. This can significantly alter release kinetics of the molecule. In the case of proteins,

alteration of the chemical nature of the side chain of amino acid residues such as a lysine, cysteine, etc., via a chemical reaction with the polymer could result in irreversible changes in the tertiary structure of the protein resulting in the denaturation of the protein. Furthermore, interaction of hydrophobic residues, such as tryptophan, in the protein backbone with hydrophobic regions in the polymer could also result in conformational changes. Conformational changes in proteins in most cases is accompanied by a loss or diminution of activity. Therefore, these problems have to be addressed in order to develop efficient delivery vehicles .

The reactivity of therapeutic agent with the polymer is of even greater concern when the polymer backbone is highly reactive as in the case of the polyanhydrides. Polyanhydrides, which belong to the class of biocompatible and biodegradable polymers, have been extensively investigated as vehicles for controlled delivery of therapeutic agents due their ability to undergo surface degradation. Tamada and Langer, *J. Biomater. Sci. Polym. Edn*, 3(4):315-353. The surface erosion of the polymer results in a zero-order release of the therapeutic agent from the polymer which is highly desirable in treatment of chronic ailments. However, the desired release kinetics can be significantly altered if the therapeutic agent of interest reacts with the polymer. Amine containing drugs and peptide hormones, such as insulin, chemically interact and react with polyanhydrides. Leong et al., *Biomed. Mat. Res*, 20: 51-64. Ron, *Proc. Natl. Acad. Sci USA*, 90: 4176-4180. In the case of insulin, denaturation of the protein during release from polyanhydride (poly(p-carboxyphenoxy hexane (CPH)) matrices was observed as indicated by the formation of aggregates. Li et al. have shown that the incorporation of caffeine base in poly(D,L-lactic acid) enhances the degradation rate of the polymer. Li et al., *J. Controlled. Rel.*, 40:41-53. Hence, there exists a need to prevent undesirable interactions between the therapeutic agent and the polymer matrix.

Numerous references disclose particles which include cyclodextrins for drug delivery. U.S. Patent No. 4,925,678 to Ranney discloses coatings and matrix materials which include drugs or diagnostic agents, such as cyclodextrin. U.S. Patent No. 5,506,203 to Backstrom et al. discloses

methods of treating patients in need of insulin treatment by administering a dry powder via inhalation along with an enhancer compound, such as a cyclodextrin. U.S. Patent No. 5,534,496 to Lee et al. discloses tablets formed with a drug trapped inside a uniform coating of peptides in a cyclodextrin matrix. U.S. Patent No. 5,582,836 to Carli et al. discloses transdermal therapeutic compositions including drugs which are incorporated into microparticles prepared from polymeric cyclodextrins. U.S. Patent No. 5,595,762 to Derrieu discloses compositions including active agents which are stabilized by coating them in film-forming agents such as polyvinyl pyrrolidones, polyvinyl alcohols, and other water-soluble polymers. The agents can then be sequestered in cyclodextrins. PCT WO 96/28143 by Boeringer Mannheim discloses polypeptide-containing microparticles which can include additives such as cyclodextrins. PCT WO 97/04747 by Dunn discloses particles for the delivery of large macromolecules, which are entrapped in biodegradable hydrogel polymers. The macromolecules can be complexed with cyclodextrins, which are then encapsulated into nanoparticles with biodegradable water-soluble hydrogel polymers.

It would be advantageous to provide drug delivery formulations wherein interactions between the drug and the polymeric material are minimized or eliminated. It would also be advantageous to provide formulations which minimize burst release of encapsulated agents.

It is therefore an object of the present invention to provide means for minimizing or reducing drug-polymer interactions in polymeric drug delivery formulations. It is a further object of the present invention to provide polymeric compositions which minimize the burst effect typically observed with many drug delivery devices.

Summary of the Invention

Compositions which include a complex of a biologically active agent and a cyclodextrin, which can be encapsulated in a polymeric microparticle or other polymeric device, and methods of preparation and use thereof are disclosed. The compositions are prepared from a water-insoluble, biodegradable polymer such as a polyanhydride, polyester, or polylactone.

The biologically active agent is an agent which includes reactive groups which could react with the polymers if they were not complexed with a cyclodextrin. In addition to minimizing or preventing interactions between the agent and the polymer, the cyclodextrin helps provide linear release of the incorporated agent rather than a burst release, acts as a surfactant to help stabilize emulsions during microparticle preparation, and allows for improved re-suspension of lyophilized microparticles relative to particles that do not include a cyclodextrin. In addition, in some cases, cyclodextrin drug complexes can be loaded to contain higher concentrations of a drug than complexes without cyclodextrin.

The devices and microparticles can be prepared using known methodology, taking care not to denature the incorporated agent. Preferred methods of preparing the microparticles are by spray drying or emulsion techniques. The devices and particles are used to deliver therapeutic, prophylactic and/or diagnostic agents to a patient in need thereof. Examples of useful drugs that can be delivered in an enhanced manner include antibiotics such as chlorhexidine and anticancer compounds such as the rhodium (II) carboxylates and their derivatives.

Brief Description of the Drawings

Figure 1 is a graph comparing release of uncomplexed chlorhexidine (white triangles), chlorhexidine complexed with beta cyclodextrin (BCD) (black diamonds), and chlorhexidine complexed with hydroxypropyl beta cyclodextrin (HPBCD) (black squares) from poly(D,L-lactic-co-glycolic acid) ("PLGA") microspheres.

Detailed Description of the Invention

Formulations have been developed based on cyclodextrin complexes which are then encapsulated in polymer. These complexes prevent reactions between the polymer and the encapsulated agent.

I. Cyclodextrin Complexes

A. Agents

Any of a variety of therapeutic, prophylactic or diagnostic agents can be complexed with a cyclodextrin for local or systematic delivery. Active agents which have a group which is potentially reactive with a polymer, for example, drugs which have amino, carboxyl, sulfhydryl, or sulfonyl groups, are particularly useful to form cyclodextrin complexes. Examples of agents include synthetic inorganic and organic compounds, proteins and peptides, polysaccharides and other sugars, lipids, and nucleic acid sequences having therapeutic, prophylactic or diagnostic activities. Nucleic acid sequences include genes, antisense molecules which bind to complementary DNA to inhibit transcription, and ribozymes. Proteins are defined as consisting of 100 amino acid residues or more; peptides are less than 100 amino acid residues. Unless otherwise stated, the term protein refers to both proteins and peptides. Examples include insulin and other hormones. The agents to be incorporated can have any of a variety of biological activities, such as vasoactive agents, neuroactive agents, hormones, anticoagulants, immunomodulating agents, cytotoxic agents, prophylactic agents, antibiotics, antivirals, antisense, antigens, and antibodies. Compounds can be of a wide range of molecular weights, for example, between 100 and 500,000 grams per mole.

The examples demonstrate complexation of an antibiotic, chlorhexidine, in a formulation which is particularly useful in treatment of periodontal disease. Rhodium(II) citrate, a transition metal anticancer compound which chelates DNA, has been complexed with a cyclodextrin, hydroxypropyl-beta-cyclodextrin as a means to improve encapsulation and release kinetics from poly(dl-lactic-co-glycolic) acid ("PLGA") and poly(anhydride) microspheres. The complexation of rhodium(II) citrate with hydroxypropyl-beta-cyclodextrin significantly increased both the encapsulation efficiency and duration of release in both polymer systems.

B. Cyclodextrins

Cyclodextrins are a family of crystalline molecules that include a chain of six, seven or eight glucopyranose units that are joined to one another

at their terminal ends. Due to steric interactions, cyclodextrins form a cyclic structure of torus-shaped macro-rings which have an internal axial cavity. The outer surface of these molecules is hydrophilic, and the internal cavity is apolar.

Cyclodextrins form complexes with various drug molecules. The complex is useful in preventing or minimizing interactions between the biologically active agent and a polymer. These interactions are particularly deleterious when the biologically active material includes reactive groups such as, for example, amine groups of a protein or peptide, and the polymer is a biodegradable polymer such as a polyanhydride, polyester, polycarbonate, or other polymer which contains functional groups which react with amine groups.

Other advantages of including a cyclodextrin in the formulation are that the cyclodextrin can act as a surfactant for the microparticles, as an emulsion stabilizer during particle preparation, and also can allow for improved re-suspension of lyophilized microparticles prior to injection. Still another advantage is that cyclodextrins can increase encapsulation efficiency (loading) of water soluble drugs in hydrophobic polymers when using double emulsion systems.

Any cyclodextrin can be used which reacts with one or more groups on the agent to be incorporated to form a complex, which acts as a suitable surfactant during the preparation of the particles, or which allows lyophilized particles to re-suspend without significant agglomeration or aggregation. The cyclodextrins are preferably pyrogen free. Suitable cyclodextrins are disclosed, for example, in PCT WO 96/20222 by Solvay, the contents of which are hereby incorporated by reference. Examples of pyrogen free cyclodextrins include alpha cyclodextrin, gamma cyclodextrin, hydroxypropyl alpha cyclodextrin, hydroxypropyl beta cyclodextrin, and hydroxypropyl gamma cyclodextrin.

The cyclodextrins can be water-soluble. Examples of water-soluble cyclodextrins include hydroxyethyl alpha cyclodextrin, hydroxyethyl beta cyclodextrin, hydroxyethyl gamma cyclodextrin, hydroxypropyl alpha cyclodextrin, hydroxypropyl beta cyclodextrin, hydroxypropyl gamma

cyclodextrin, methylated beta cyclodextrin, trimethyl beta cyclodextrin, tertiary amine beta cyclodextrin, sulfated alpha cyclodextrin, sulfated beta cyclodextrin, sulfated gamma cyclodextrin, and sulfated delta cyclodextrin.

The cyclodextrins can be water-insoluble. Examples of water-insoluble cyclodextrins include acetylated alpha cyclodextrin, acetylated beta cyclodextrin, acetylated gamma cyclodextrin, hexylated beta cyclodextrin, 2-ethylhexylglycidyl ether beta cyclodextrin, C-6 monohexyl sulfide beta cyclodextrin, C-6 mono-para-toluene sulfonate beta cyclodextrin.

The cyclodextrins can be anionic. Examples of anionic cyclodextrins include sulfated beta cyclodextrin, sulfated alpha cyclodextrin, sulfated gamma cyclodextrin, octenylsuccinylated beta cyclodextrin, carboxymethyl alpha cyclodextrin, carboxymethyl beta cyclodextrin, succinylated beta cyclodextrin.

The cyclodextrins can be cationic. Examples of cationic cyclodextrins include quaternary ammonium alpha cyclodextrin, quaternary ammonium beta cyclodextrin, and quaternary ammonium gammacyclodextrin.

The cyclodextrins can also be amphoteric. Examples of amphoteric cyclodextrins include quaternary ammonium carboxymethyl beta cyclodextrin and tertiary amine carboxymethyl beta cyclodextrin.

Preferred cyclodextrins are methylated cyclodextrins, hydroxypropyl cyclodextrins, hydroxyethyl cyclodextrins, quaternary ammonium cyclodextrins, and sulfated cyclodextrins. Most preferred are hydroxypropyl cyclodextrin and quaternary ammonium cyclodextrins.

C. Polymeric Composition

Polymeric compositions may be formed from any biocompatible, and preferably biodegradable, polymer, copolymer, or polymer blend. Preferred polymers are those which are capable of degrading *in vivo* over a course of hours to months, depending on the desired rate of drug delivery. The polymers may be tailored to optimize different characteristics of the particle including: i) interactions between the agent to be delivered and the polymer to provide stabilization of the agent and retention of activity upon delivery; ii) rate of polymer degradation and, thereby, rate of drug release profiles; iii)

surface characteristics and targeting capabilities via chemical modification; and iv) device porosity.

Surface eroding polymers such as polyanhydrides may be used to form the particles. For example, polyanhydrides such as poly[(*p*-carboxyphenoxy)-hexane anhydride] (PCPH) may be used. Biodegradable polyanhydrides are described in U.S. Patent No. 4,857,311, to Domb et al., the contents of which are incorporated herein by reference.

In another embodiment, bulk eroding polymers such as those based on polyesters, including poly(hydroxy acids) can be used. For example, polyglycolic acid (PGA), polylactic acid (PLA), or copolymers thereof may be used to form the particles. The polyester may also have a charged or functionalizable group, such as an amino acid. In a preferred embodiment, particles with controlled release properties can be formed of poly(D,L-lactic acid) and/or poly(D,L-lactic-co-glycolic acid) ("PLGA") which incorporate a surfactant such as dipalmitoyl phosphatidylcholine ("DPPC").

Other useful polymers include polyamides, polycarbonates, polyalkylenes such as polyethylene, polypropylene, poly(ethylene glycol), poly(ethylene oxide), poly(ethylene terephthalate), poly vinyl compounds such as polyvinyl alcohols, polyvinyl ethers, and polyvinyl esters, polymers of acrylic and methacrylic acids, polyphosphates, polyphosphonates, polyorthoesters, polyphosphazenes, celluloses and other polysaccharides, and peptides or proteins, or copolymers or blends thereof. Polymers may be selected with, or modified to have, the appropriate stability and degradation rates *in vivo* for different controlled drug delivery applications. Materials other than biodegradable polymers may be used to form the particles. Suitable materials include various non-biodegradable polymers and various excipients.

D. <u>Other Components</u>

Excipients

In addition to the encapsulated complex, the device can include one or more excipients such as a sugar, such as lactose, a protein, such as gelatin or albumin, and/or a surfactant.

Surfactants

As used herein, the term "surfactant" refers to any agent which preferentially absorbs to an interface between two immiscible phases, such as the interface between water and an organic polymer solution, a water/air interface or organic solvent/air interface. Surfactants generally possess a hydrophilic moiety and a lipophilic moiety, such that, upon absorbing to microparticles, they tend to present moieties to the external environment that do not attract similarly-coated particles, thus reducing particle agglomeration. Surfactants may also promote absorption of the encapsulated agent and increase bioavailability of the agent.

As used herein, a particle "incorporating a surfactant" refers to a particle with a surfactant on at least the surface of the particle. The surfactant may be incorporated throughout the particle and on the surface during particle formation, or may be coated on the particle after particle formation. The surfactant can be coated on the particle surface by adsorption, ionic or covalent attachment, or physically "entrapped" by the surrounding matrix. The surfactant can be, for example, incorporated into controlled release particles, such as polymeric microspheres. Providing a surfactant on the surfaces of the particles can reduce the tendency of the particles to agglomerate due to interactions such as electrostatic interactions, Van der Waals forces, and capillary action. The presence of the surfactant on the particle surface can provide increased surface rugosity (roughness), thereby reducing the surface area available for intimate particle-particle interaction.

Surfactants known in the art can be used including any naturally occurring surfactant. Other exemplary surfactants include phosphogycerides; hexadecanol; fatty alcohols such as polyethylene glycol (PEG); polyoxyethylene-9-lauryl ether; a surface active fatty acid, such as palmitic acid or oleic acid; sorbitan trioleate (Span 85); glycocholate; surfactin; a poloxomer; a sorbitan fatty acid ester such as sorbitan trioleate; tyloxapol and phospholipids.

II. Formation of Polymeric Devices

Polymeric devices may be prepared using standard techniques. In the preferred embodiment, the devices are particles, between 25 and 1000 μm in diameter. These particles can be formed by single and double emulsion solvent evaporation, spray drying, solvent extraction, solvent evaporation, phase separation, simple or complex coacervation, interfacial polymerization, or other methods well known to those of ordinary skill in the art. Preferred methods for preparing the particles are spray drying and double emulsion techniques.

Methods developed for making microspheres for delivery of encapsulated agents are described in the literature, for example, as described in Doubrow, M., Ed., "Microcapsules and Nanoparticles in Medicine and Pharmacy," CRC Press, Boca Raton, 1992. Methods also are described in Mathiowitz and Langer, *J. Controlled Release*, 5:13-22 (1987); Mathiowitz *et al.*, *Reactive Polymers*, 6:275-283 (1987); and Mathiowitz *et al.*, *J. Appl. Polymer Sci.*, 35:755-774 (1988). The selection of the method depends on the polymer selection, the size, external morphology, and crystallinity that is desired, as described, for example, by Mathiowitz *et al.*, *Scanning Microscopy*, 4: 329-340 (1990); Mathiowitz *et al.*, *J. Appl. Polymer Sci.*, 45:125-134 (1992); and Benita *et al.*, *J. Pharm. Sci.* 73:1721-1724 (1984).

Solvent evaporation is described, for example, in Mathiowitz *et al.*, (1990), Benita; and U.S. Patent No. 4,272,398 to Jaffe. With some polymeric systems, polymeric particles prepared using a single or double emulsion technique vary in size depending on the size of the droplets. If droplets in water-in-oil emulsions are not of a suitably small size to form particles with the desired size range, smaller droplets can be prepared, for example, by sonication or homogenization of the emulsion, or by the addition of surfactants. Methods of spray drying are disclosed in PCT WO 96/09814 by Sutton and Johnson.

If the particles prepared by any of the above methods have a size range outside of the desired range, particles can be sized, for example, using a sieve, and further separated according to density using techniques known to those of skill in the art.

III. Drug Administration

The polymeric composition may be administered alone or in any appropriate pharmaceutically acceptable carrier, such as a liquid, for example saline, or as a powder. Devices can be implanted or injected. Particles can be administered via injection, for example, subcutaneous, intravenous, intraperitoneal, or intramuscular injection, orally, via inhalation, transmucosally, or other means known to those of skill in the art. Appropriate dosage, formulations and delivery systems may be selected for a particular application, taking into consideration the dosage regimens and other pertinent information.

In one preferred embodiment, the agent that is complexed with the cyclodextrin and formed into the microparticle is one that is useful for the treatment or prophylaxis of periodontic disease. An example of such an agent is an antibiotic, chlorhexidine, although other useful agents are well known to those of skill in the art. The microspheres are administered to the mucosal tissue surrounding the teeth.

The present invention will be further understood by reference to the following non-limiting examples.

Example 1: Chlorhexidine Release from PLGA Microspheres

Inclusion complexes of chlorhexidine and beta cyclodextrin (BCD) and hydroxypropyl beta cyclodextrin (HPBCD) were prepared by freeze drying a 1:1 molar ratio of digluconate of chlorhexidine and the cyclodextrin. PLGA microspheres including chlorhexidine alone and which include the two complexes were prepared by double emulsion (w/o/w)/solvent evaporation technique: O'Donnell and McGinity, *Advance Drug Delivery Reviews*, 25-42 (1997). The microspheres were characterized for size and morphology using a Coulter Counter particle sizer and by Scanning Electron Microscopy. The average particle size of the microspheres was 30 µm for chlorhexidine alone, 15 µm for the BCD complex, and 10 µm for the HPBCD complex.

The release of chlorhexidine from the microspheres was evaluated, and the results are shown in Figure 1. Microspheres including uncomplexed

chlorhexidine (white triangles) showed a large burst effect (43% of loading), whereas the microspheres including complexed chlorhexidine (black diamonds and black squares) showed a negligible burst effect.

Chlorhexidine complexed with BCD (black diamonds) demonstrated release over a longer period of time than chlorhexidine complexed with HPBCD (black squares). This data demonstrates that inclusion complexes of drugs and cyclodextrins can be used to deliver the complexed drugs in a controlled manner without a burst effect.

We claim:

1. A polymeric composition comprising an agent complexed with a cyclodextrin which is dispersed within a polymer wherein the agent comprises groups reacting with groups on the polymer and these groups on the agent are complexed with cyclodextrin.

2. The composition of claim 1 wherein the polymer is selected from the group consisting of polyhydroxy acids, polyanhydrides, polyorthoesters, polyesters, polyphosphazenes, and copolymers and blends of these polymers.

3. The composition of claim 1 wherein the polymer is non-biodegradable.

4. The composition of claim 1 in the form of microparticles.

5. The composition of claim 1 wherein the agent contains groups reactive with the polymer selected from the group consisting of amino, carboxyl, sulfhydryl, and sulfonyl groups.

6. The composition of claim 1 wherein the cyclodextrin is selected from a group consisting of pyrogen free, water-soluble, water-insoluble, anionic, cationic, and amphoteric cyclodextrins.

7. The composition of claim 1 further comprising an excipient or a surfactant.

8. The composition of claim 1 wherein the release of the incorporated agent approximates zero order or first order release.

9. The composition of claim 1 wherein the agent is a drug.

10. A method for delivering an agent to a patient in need thereof wherein the agent is complexed with a cyclodextrin which is dispersed within a polymer wherein the agent comprises groups reacting with groups on the polymer and these groups on the agent are complexed with cyclodextrin.

11. The method of claim 10 wherein the polymer is in the form of a microparticle.

12. The method of claim 11 wherein the microparticles are administered by injection.

13. The method of claim 11 wherein the microparticles are administered orally.

14. The method of claim 11 wherein the microparticles are administered topically.

15. The method of claim 11 wherein the polymer is selected from the group consisting of polyhydroxy acids, polyanhydrides, polyorthoesters, polyesters, polyphosphazenes, and copolymers and blends of these polymers.

16. The method of claim 11 wherein the agent contains groups reactive with the polymer selected from the group consisting of amino, carboxyl, sulfhydryl, and sulfonyl groups.

17. The method of claim 11 wherein the cyclodextrin is selected from a group consisting of pyrogen free, water-soluble, water-insoluble, anionic, cationic, and amphoteric cyclodextrins.

18. The method of claim 11 wherein the agent is selected from a group consisting of synthetic inorganic and organic compounds, proteins and peptides, polysaccharides and other sugars, lipids, and nucleic acid sequences.

19. The method of claim 11 wherein the agent is delivered for the treatment of periodontal disease.

20. The method of claim 18 wherein the agent is a anti-cancer therapeutic.

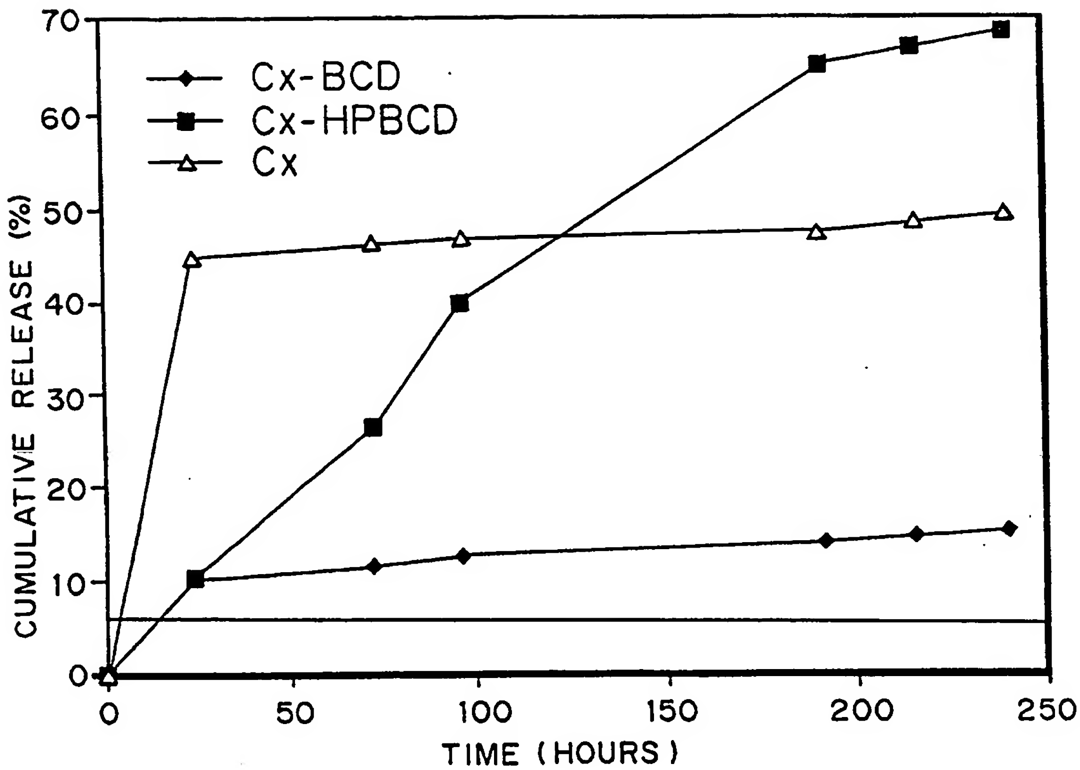
70
60
50
40
30
20
10
0
CUMULATIVE RELEASE (%)
Cx-BCD
Cx-HPBCD
Cx
0
50
100
150
200
250
TIME (HOURS)

FIG. 1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/11981

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	SINISTERRA, RUBEN DARIO ET AL: "Encapsulation and Release of Rhodium(II) Citrate and Its Association Complex with Hydroxypropyl-.beta.- cyclodextrin from Biodegradable Polymer Microspheres" J. PHARM. SCI. (1999), 88(5), 574-576, XP000823551 see the whole document ---	1-20
Y	WO 95 11665 A (VIRBAC LAB ;DERRIEU GUY (FR); AUBERT ANDRE (FR); RAYNIER BERNARD () 4 May 1995 see the whole document; claims; example 1 ---	1-20
X,Y	EP 0 745 381 A (TECNIMEDE SOCIEDADE TECNICO ME) 4 December 1996 see the whole document; claims; example 1 ---	1-20
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 September 1999	23 September 1999 (23.09.99)

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	BERTE, M

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/11981

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 241 806 A (FUJISAWA PHARMACEUTICAL CO) 21 October 1987 see the whole document; claims; example 1 ---	1-20
X	EP 0 193 164 A (FUJISAWA PHARMACEUTICAL CO) 3 September 1986 see the whole document; claims; example 1 -----	1

1

INTERNATIONAL SEARCH REPORT

I ational application No.
PCT/US 99/ 11981

Box I Observation where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 10-20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

.ormation on patent family members

Interr ·onal Application No
PCT/US 99/11981

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 9511665	A	04-05-1995	FR	2711525	A	05-05-1995
			AT	181500	T	15-07-1999
			AU	688408	B	12-03-1998
			AU	8109294	A	22-05-1995
			CA	2175077	A	04-05-1995
			DE	69419260	D	29-07-1999
			DE	725627	T	30-04-1997
			EP	0725627	A	14-08-1996
			ES	2095819	T	01-03-1997
			JP	9505564	T	03-06-1997
			NZ	275837	A	24-11-1997
			US	5683722	A	04-11-1997
EP 0745381	A	04-12-1996	NONE			
EP 0241806	A	21-10-1987	JP	63045219	A	26-02-1988
			US	4749574	A	07-06-1988
EP 0193164	A	03-09-1986	JP	62000015	A	06-01-1987